DIFFUSE DEGENERATION OF THE SPINAL CORD.*

Clinical Analysis of Fifty Cases.

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Pathological Study of Five Cases.

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(From the Sears Pathological Laboratory, Harvard Medical School.)

(Continued from page 21.)

PATHOLOGICAL REPORT, BY DR. TAYLOR.

The details of the pathological examination of five cases of diffuse degeneration are herewith given, with the essential features of the clinical histories, so far as they are obtainable:

Case I.—This patient, who at the time of his death was a man of fifty-five, had been under the medical observation of one of the writers for many years before the onset of the anemic and spinal symptoms which led to his death.

The family history, which was of much interest, has already been indicated in the earlier part of this paper. Let it suffice to say here that in the large family to which he belonged, tuberculosis, cancer, interstitial nephritis, and a highly psychopathic tendency had figured largely, associated with brilliancy, talent, and fine personal traits.

The patient himself, though always excitable and unstable, had been a successful man of business. Gradually, his nervous instability gained the upper hand, morbid fears and a tendency to outbreaks of passion showed themselves, and for many years before his death he made himself an exile at his country place. His physical health had never been vigorous, and digestive troubles of slight degree were of frequent occurrence. Between three and four years before his death it became noticeable that his complexion and skin were at times very sallow, even icteric. These periods seemed, as a rule, to attend or follow periods of depression or excitement, and might then pass quickly away. Little by little, however, the sallowness became more permanent, and was associated with marked pallor. Three years before his death he was induced to make a trip to Europe, and while absent Dr. H. C. Baldwin, who accompanied him, noted an anemic murmur over the heart, which afterwards increased. Within two years before his death all the symptoms became more pronounced. Bleeding of the gums set in and became a troublesome symptom. Arsenic at first relieved him greatly in all respects, or seemed to do so, but the improvement was only temporary. A blood examination made by Dr. J. J. Thomas about nine months before his death gave the following result: Hb., 26 per cent.; reds, 1,284,000; whites, 3,750; polynuclear whites, 49.6 per cent.; large mononuclear, 20.5 per cent.; small lymphocytes, 27.2 per cent.; eosinophiles, 2.7 per cent.; poikilocytosis; numerous nucleated reds. The spinal symptoms came on gradually during the last year of his life, and consisted first in a feeling of numbness in the extremities, then in increasing weakness and inco-ordination, which, however, never reached a high degree. There was general emaciation and flabbiness of the muscles. Death came on gradually, with increasing exhaustion. The autopsy was made by Dr. W. F. Whitney, who found, besides extreme anemia of all the tissues, pigmentation of the liver (deposition of iron), and characteristic changes in the bone marrow.

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Microscopic Examination.—Spinal cord alone examined. Stained by Weigert hematoxylin; carmine; carmine hematoxylin. The degenerations in this case are confined essentially to the dorsal and lateral regions of the cord, and are more marked in the upper than in the lower segments.

Lumbar Enlargement.—The degenerations in this region are exceedingly slight, as shown by the Weigert myeline sheath method. Throughout the dorsal columns there is a distinct diminution in the amount of staining myeline, with a proportionate increase in neuroglia elements: (Carmine-hematoxylin preparation.) The neuroglia septa are markedly increased in caliber, and the individual neuroglia cells are large. A similar change, but much less in degree, may be made out in the lateral tracts, occupying in a general way, but not sharply limited to, the pyramidal tracts. A section made slightly higher, lower thoracic region, shows a much more marked degeneration in the areas already named. Especially marked are two tongue-shaped areas in the dorsal tracts, placed symmetrically on either side of the dorsal septum. These areas show an almost complete disintegration of myeline and axones, with an imperfect compensatory proliferation of neuroglia.

Thoracic Region.—The thoracic cord at various heights from below upwards shows progressively more marked degenerations in the dorsal and lateral columns, of the general type described above. The small tongue-shaped areas seen in the lower thoracic region become larger and show a tendency to coalesce in the dorso-median tract (Goll.). An area corresponding to the direct cerebellar tract is spared, in a part, at least, of the thoracic cord. There is no degeneration of the ventral tracts bordering the ventral fissure.

Cervical Region.—The degenerations still fairly sharply delineated are here more marked and extensive than at lower levels of the cord. The cerebellar tract is invaded on both sides to a certain degree; the dorsal tracts show a complete degeneration, with the exception of a narrow strip in the lateral portion of the dorso-external columns (Burdach) bordering the horns. The ventral white matter remains wholly uninvolved.

Gray Matter.—There is no evidence of an active degenerative process in the ventral horns. The lumbar enlargement shows many hyperpigmented cells, which, in the present state of our knowledge, must be regarded as a disorder of metabolism, the pathological significance of which is obscure. In the cervical region the motor cell bodies are fewer in number than one would expect, and show in certain instances distinct degenerative changes. The dorsal horns show nothing abnormal beyond an equally noticeable pigmentation of the cells of Clarke's column.

Nerve Roots.—In general the nerve roots, both dorsal and ventral, are not degenerated, though occasionally somewhat imperfectly staining bundles may be made out. The dorsal roots at no point show the changes which are an essential part of the pathological process in tabes.

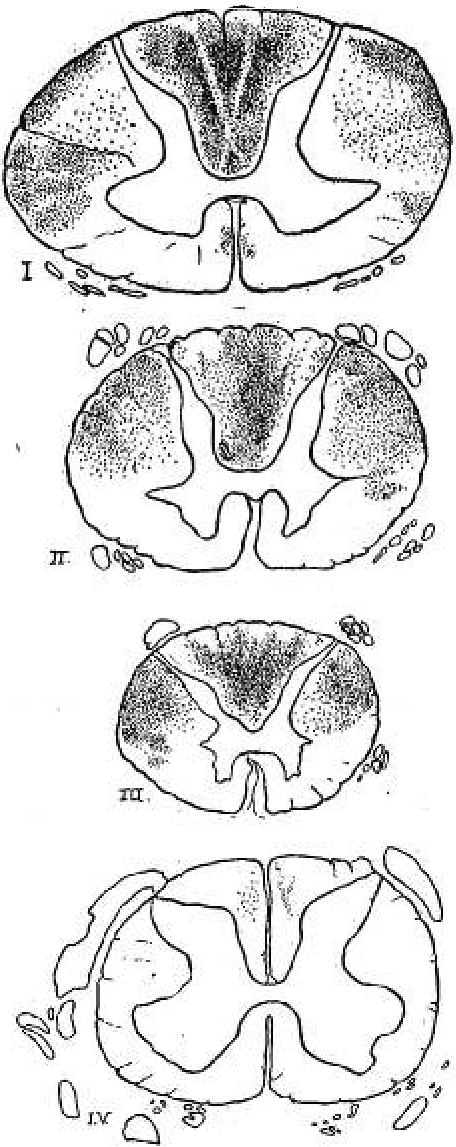
Blood Vessels.—Many of the vessels within the cord have moderately thickened walls, in a condition of hyaline degeneration. The pia and its contained vessels are normal.

Summary.—Diffuse degeneration of dorsal and lateral tracts of cord, not sharply confined to recognized neurone systems; degeneration more marked in upper than in lower segments of the cord; slight nerve cell changes; insignificant degeneration in the nerve roots; hyaline degeneration of vessel walls.

Case II.—The patient, a lady, at the age of fifty-two came under the care of Dr. E. M. Buckingham, to whose courtesy the following notes are due. She had *always been anemic, easily worried and overworked, and had had a real and constant cause of worry for many years.* In 1882 she had a fall, striking on her back, and in 1883 a long continued and severe bronchitis. In 1890 she had considerable diarrhea and nausea, which continued off and on for six months, when she had grippe, and this in its turn was again followed by nausea and diarrhea. In 1892 she had a severe hemorrhage from some part of the urinary passages, and after this was severely blanched for many months. From this time to 1896, when she died, nausea and vomiting, induced by fatigue or worry, were of frequent occurrence. During this period "numbness" of the arm was occasionally complained of, and in 1895 this symptom was specifically noted as affecting the legs and sometimes extending as high as the waist, though the slightest touch from another person's finger was felt in the affected parts. On April 16 of this year the blood was examined for pernicious anemia, but with negative results. Tremor in the left and then in the right arm was next noted. The pupils were found to have a normal reaction. She died finally on June 8, 1896, from exhaustion, due mainly to the continued attacks of vomiting. The urine had been examined many times by Dr. Buckingham and others, but without showing any traces of albumin or casts. Nevertheless (as in Case IV.) the kidneys were found, post mortem, to show signs of interstitial disease by Dr. Mallory. Edema had, however, been noted before this. The prolonged gastric symptoms in this case again recall to mind some of the statements in the paper by Dr. Adami above referred to, though the liver and spleen were found normal after death, as they had appeared to be on repeated examination during life.

Microscopic Examination.—Spinal cord examined; stained by Weigert hematoxylin; Marchi, Van Gieson; phosphomolybdic acid (Mallory.) The degeneration of white matter in this case is distributed chiefly through the dorsal and lateral tracts, with slight involvement of the ventral white matter. It is most pronounced in the cervical region.

Lumbar Enlargement.—The cord at this region presents an absolutely normal appearance of the white matter, with the exception of exceedingly small areas of degeneration in the dorsal columns on either side of and at a little distance from the dorsal septum, and also two areas, still less marked, in the region of the pyramidal tracts. These areas present the peculiar, vacuolated appearance later to be described more in detail, which there is some reason to think is characteristic of the type of process under discussion. The reticulum of myelinated axones and collaterals in the ventral horns are stained (Weigert) with distinctness and show no pathological defect.



Diagrams of the Spinal Cord from Case II.

Thoracic Region.—In the thoracic region the degeneration has extended in a diffuse manner without definite relation to neurone systems over a large part of the dorsal columns, and the lateral tracts, sparing the ventral ground bundles, the area occupied by Gowers' tract, and the ventro-lateral ground bundles. The degenerated areas show numerous vacuoles, probably distended and disintegrating myeline sheaths, with no overgrowth of neuroglia, hence giving in Weigert sections a much less marked color contrast than ordinarily seen. Marchi slides show an enormous number of fat droplets throughout the degenerated areas, the product of disintegrating myeline, leading to the formation of fat granule cells. (Plate I., Fig. 1.)

Cervical Region.—The degeneration here is considerably more extensive than at lower levels. The dorsal columns are completely involved, excepting for a peripheral layer of normal fibers on the dorsal aspect of the cord and along the horns on either side, extending ventrally to the region of the dorsal commissure, in the immediate neighborhood of which fibers are also spared, as is usual, for example, in tabes. A point of interest also is the fact that a very narrow strip of essentially normal fibers divides on both sides the dorso-median (Goll) from the dorso-lateral (Burdach) columns, and that these lines of demarcation also separate two distinct varieties, or at least stages, of degeneration. (Plate I., Fig. 2.) Occupying the greater part of the median tract is a dense neuroglia sclerosis, of the type commonly seen in the cord compensatory to systemic neurone degenerations. Outside of these narrow limits, however, in the external dorsal columns, the peculiar type of change, to which we have already alluded, is predominant. The section is riddled with vacuoles of varying sizes, certainly not to be regarded as artefacts, since the change is sharply confined to the degenerated areas. It is further noteworthy that the vacuolated areas, in sections stained with osmic acid, show a very marked preponderance of fat over the dense sclerosis of the median column, indicating, no doubt, an earlier stage of degeneration. As remarked in the case already described, it is noticeable also here that in large areas of the degenerated portions the neuroglia shows no tendency to proliferate, giving the diseased areas a sieve-like appearance. (Plate I.) This fact we are inclined to think is of some importance in the proper interpretation of the nature of the pathological change under consideration. The lateral tracts of the cord in the cervical region are involved as in the thoracic region without respect to fiber tracts, but somewhat more extensively. The region of the cerebellar tract is particularly involved; that of the pyramidal tract less so. A very slight degeneration occurs in the ventral portion of the cord on both sides of the fissure.

Gray Matter.—Normal except for over-pigmentation and other changes of ventral horn cells. In many cases the entire cell-body is filled with pigment; in others the nuclei have disappeared, apparently as a result of the encroachment of the pigment. Nuclei are in some instances distorted in shape, and frequently have lost their distinct outline. Many cells show an absence of granulation. A considerable number of cells are still to be regarded as normal. Cells of the dorsal horns also show a marked hyperpigmentation. An interesting group lying at the tip of one dorsal horn in the lumbar region shows the cell-bodies almost completely filled with pigment, the nuclei in those cells in which they are still visible placed excentrically and distorted in contour.

Nerve Roots.—The roots, both ventral and dorsal, are normal. The changes in ventral horn cells just described, whatever functional significance they may have, are evidently not sufficiently grave to lead to organic changes to an observable degree in their associated nerve roots.

Blood Vessels.—No noteworthy changes; pia normal.

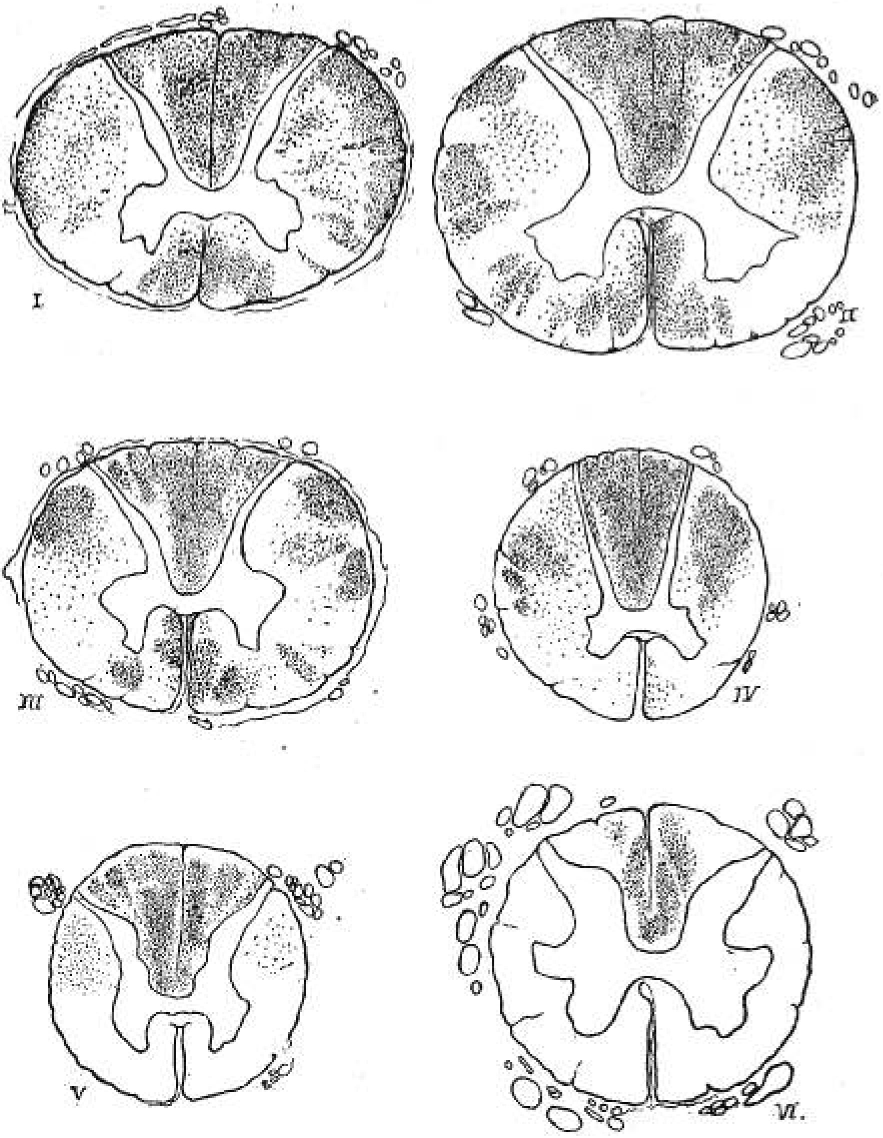
Summary.—Diffuse degeneration of cord, most extreme in cervical region; definite alterations in nerve cell-bodies; no nerve root degeneration; no abnormality of vessels.

Case III.—This patient, who was seen in consultation by Dr. Putnam with Dr. Horace E. Marion, of Brighton, was a man of fifty-four, whose occupation was that of superintendent of streets. He was of good habits and free from any suspicion of constitutional disease. Examinations were made on July 10, 1894, and October 5, 1895. The illness had begun only eight or ten weeks before the first of these examinations with a feeling of sensitiveness and numbness of the hands. He reported that if he grasped anything a feeling of thrill or shock would run through the hands and arms, and even into the chest and back. At that time the legs were not involved, and the knee-jerks were present, but slightly developed. The numbness of the hands was associated with a disability in their use so great that he could with difficulty feed himself. Walking caused fatigue, but otherwise was normal. The urine had been examined and a trace of arsenic found, associated with signs of irritation of the kidney. The grasp of the right hand was excessively feeble, and both hands and arms showed slight degrees of atrophy of some of the hand and forearm muscles, with quantitative changes in the electrical reactions. The patient improved in the use of his hands, as so often happens, but after a time similar sensory symptoms appeared in the feet, legs, perineum, and genitals, associated with rapidly increasing loss of muscular power. Shortly before the second examination he had been confined to the bed with an attack of vomiting and diarrhea, and when this was over he found himself at first unable to get up because of muscular weakness. The sensibility of the rectum was diminished and there was slight objective loss of the sense of contact in the feet, associated with a hyperesthesia which made it uncomfortable for him to be handled. There was also a well-marked sense of constriction about the legs. The micturition had become slow and difficult. The knee-jerk was present on both sides and rather greater than is common in health, and the Achilles reflex was also slightly exaggerated. The Romberg sign was present in a slight degree. The nutrition was poor, the face was sallow in color and the Hb. was found to be 65 per cent. The patient continued to lose ground gradually and died in complete paraplegia.

Microscopic Examination.—Cord examined. Stained by Weigert hematoxylin; Van Gieson, hematoxylin-picric-acid-fuchsin; Mallory-phosphomolybdic acid. This case resembles, in general, the foregoing in its pathological anatomy, but shows a still more extensive process, likewise of greatest intensity in the cervical region.

Lumbar Enlargement (Plate II., Fig. 4).—Sections through the sacral region show no abnormality of white or gray matter. In the lumbar enlargement there is a very marked, irregularly distributed degeneration in the dorsal columns, the lateral tracts and other portions of white matter remaining uninvolved. The type of degeneration is a combination of the ordinary neuroglia sclerosis and the non-proliferative variety already described. In this region the degeneration occupies a central position, nowhere reaching the dorsal periphery, nor the surrounding gray matter of the horns and commissure. At a slightly higher level the areas of degeneration are diminished in size and still confined to the dorsal tracts. At the transitional portion between the thoracic and lumbar cord the degeneration of the dorsal tracts is again more extensive, and distributed in more or less discrete patches. A slight degeneration in the lateral columns, in the neighborhood of the motor tract, is observable. Other portions of the cord are not involved.

Thoracic Region.—Throughout this region, varying somewhat at different heights, the degenerated areas involve the dorsal tracts, as already described, occasionally reaching to the periphery. The area of the pyramidal tracts and outlying por-



Diagrams of the Spinal Cord from Case III.

tions of the lateral white matter are very markedly degenerated. There are also occasional small islets of degeneration in the ventral columns, and also in the ventro-lateral white matter. The degeneration is nowhere sharply confined to neurone tracts.

Cervical Region (Plate II, Fig. 3).—Both in the lateral and dorsal columns, as well as in other portions of the cord, the process here reaches its greatest intensity. Sections present a widely extended and very diffuse degeneration, involving in addition to the areas described above, a considerable portion of the ventral white columns, and in patches the contiguous white matter back to the chief areas of degeneration in the lateral tracts. Excepting a fairly dense neuroglia overgrowth in a part of the dorsal columns, the type of degeneration is the one characterized by the non-proliferation of neuroglia and the formation of vacuoles.

Gray Matter.—Beyond a considerable pigmentation of certain cells of the ventral horns, which is probably within normal limits, nothing noteworthy is observed.

Nerve Roots.—The roots, both dorsal and ventral, are, for the most part, normal. Occasionally a somewhat circumscribed area of partial degeneration may be made out (Plate II, Fig. 4), suggesting very strongly a local disturbance of nutrition rather than a primary disorder of groups of neurones. This is further borne out by the fact that the root zone is essentially intact throughout the cord.

Blood Vessels.—Beyond the fact that the smaller vessels are in general distended with blood, and hence more conspicuous than normal, they show no abnormality. The larger vessels, *e. g.*, ventral artery of cord, show no sclerotic changes. Pia normal.

Neuroglia.—The neuroglia in this, as in the foregoing case, is of special interest, from the fact that it shows small tendency to proliferate in areas which have undergone the most extensive degenerations. There is no thickening of the circumferential layer, as ordinarily seen in chronic cord diseases.

Summary.—Diffuse degeneration of white matter of cord, most marked in the cervical region. Gray matter uninvolved; dorsal nerve roots slightly degenerated in patches; blood-vessels normal.

Case IV.—This patient was a woman of fifty-six, who was under the care of one of the writers off and on for twelve years. Her family history has also been alluded to in the earlier part of the paper, and is of importance from the fact that her older sister had died, after a lingering illness, with paralysis and a high degree of contracture of both legs. The tendon reflexes had been greatly exaggerated, and attempts at voluntary motion had been associated with tremors, or irregular muscular movements. There had been, however, no disorders of speech. The mental condition had been from time to time impaired. Both of the sisters were small in stature, of slender build and of delicate health. The patient was remarkable for pallor all her life long, and likewise for her eccentric disposition, associated with great energy and other fine qualities. Throughout the long period of her illness the most prominent symptom, until later years, was an extreme sense of numbness in the hands, feet and legs. It is interesting to note that this began during a prolonged and prostrating illness from boils on the legs, abdomen and thorax, with which she had been confined to the bed. This occurred about one year before my (Putnam's) attendance began. The first seat of the numbness was the inner side of the left great toe, where it was felt as a sense of tingling. Gradually both feet and the hands became involved. At first careful tests failed to reveal any objective loss of sensibility, but it may be remarked with regard to this statement, which one hears so often made in the reports of these cases, that it probably indicates insufficient means of observation, for the patient herself had found that she could not distinguish textures as well as before her illness began. At times the feet felt excessively cold. The knee-jerk was absent, and remained so throughout her illness. The Romberg symptom at that time was not present, and there was no sign of unusual lack of strength or motor inco-ordination. For many years the condition of the patient remained about the same, as regards the nervous symptoms, which did not improve even with temporary improvements in the general health. Within the last two or three years of her life, however, gradually increasing muscular weakness and ataxia came on. Constipation and an insufficiency of the digestive powers were fairly marked features of the case, though never present to a high degree. The urine was repeatedly examined, but the records are, unfortunately, not at hand. No reason had been found to justify, it was thought, a diagnosis of chronic interstitial nephritis. Death occurred from an attack of bronchial pneumonia, associated with a serious affection of the bladder, at a time when the patient was in a very feeble state, though with a perfectly clear mind. The autopsy was made by Dr. F. B. Mallory, who rendered the following report:

Body slender, muscles small, fair amount of subcutaneous fat tissue. Brain soft, nothing abnormal seen on gross examination. Cord, evidences of degeneration in the dorsal column of the thoracic and cervical regions. Heart flabby, small, fatty degeneration. Lungs, marked edema, with a number of areas of purulent bronchial pneumonia. Spleen soft, pulp increased. Kidneys much diminished in size, capsule adherent, surface granular, fatty degeneration. Bladder extensive, diphtheritic cystitis, most marked at the neck, where there was considerable loss of substance due to ulceration.

Microscopic Examination.—Cord, oblongata, cerebral cortex, peripheral nerves, examined. Stained by Weigert hematoxylin and hematoxylin-eosin.

The degenerations of the cord in this case are diffuse in character and slight in extent, confined to the dorsal columns and less in degree to the lateral tracts.

Lumbar enlargement and region below. Slight but distinct degeneration in the dorsal columns, sparing the root zones and the commissural fibers adjoining the dorsal commissure. The lateral tracts show a very slight myeline degeneration, not limited to the pyramidal tract.

Thoracic Region.—In general similar areas of degeneration, varying somewhat at different heights and most marked in the dorso-median columns.

Cervical Region.—Similar degenerations.

Gray Matter.—The cells of the ventral horns show an excessive pigmentation.

Nerve Roots.—For the most part normal, both ventral and dorsal. At certain points, however, there is a distinct but not extensive degeneration of dorsal roots, of a character which suggests a local cause rather than a part process in a true neurone degeneration.

Blood Vessels.—The vessels either without or within the cord show no noteworthy change.

Neuroglia.—The character of the neuroglia overgrowth is not of the type described, for example, in Cases II. and III. The degeneration of myeline is slight in degree, even in the most degenerated areas, and the neuroglia has in general made good the deficiency. The limiting layer of neuroglia is of interest in the fact that at many points it shows a considerable widening.

Oblongata.—Normal. Cerebral cortex, normal.

Peripheral Nerves.—Median or internal saphenous, no noteworthy change. There is in a Weigert section a slight irregularity in the myeline staining, probably due to postmortem change rather than to a true degeneration.

Summary.—Slight degenerations of dorsal and lateral tracts, not limited to recognized neurone systems; slight changes in dorsal nerve roots; vessels, normal; oblongata, cerebral cortex, peripheral nerves, normal.

Case V.—This patient was a woman of fifty who had been examined at different periods by both the writers and by other physicians, whose observations will be in a measure referred to.

It was said that she had always been pale in color and somewhat self-willed and excitable in disposition, though otherwise in fairly good health until about four years before the first examination was made. Two years previously to that she had sustained a severe loss in the death of a near relative, to whom she was deeply attached, and on whose companionship, in fact, she was very dependent, and it is probable that the severe shock of this experience was the immediate cause of her later illness. The prostration of this shock was followed, after a time, by a tendency to insomnia, and this by a gradual loss of flesh and color. Even as long as three years before our first examination she began to notice "thrilling" sensations in the ends of the fingers when struck together, and also "drawn" feelings in the hips and knees, and across the abdomen on going upstairs. This last feeling was increased by walking, which she consequently used to dread. These paresthesias were followed after a year by gradually increasing difficulty in walking and in the use of the hands, at first mainly of ataxic character, finally paralytic. The whole duration of the motor symptoms was about two years. In the last year, or year and a half, of her life both the anemia and the nervous symptoms, including the mental excitability, steadily gained ground. Two blood examinations made respectively about six and three months before her death showed a reduction of the red cells to about 2,000,000, and the Hb to 40 per cent. There was also well-marked poikilocytosis and megalocytosis. As regards the mental condition, it may be said that at quite an early period in her illness she had had a difficulty in expressing herself, which does not appear to have been due to a localized cerebral lesion, but rather to the anemic condition of the brain. This did not return in a distinct form, though when fatigued or embarrassed she would sometimes have slight trouble in finding her words. In general her memory remained good, but she was subject to violent outbreaks of passion under slight provocation, and showed considerable lack of judgment as to her own condition and her obligations to those around her. Except in these respects, she retained a high degree of keenness to the last, even at a time when she was bloodless from pallor and scarcely capable of a movement of hand or foot. Toward the end the limbs became extremely edematous.

The body and nervous system at autopsy showed nothing remarkable beyond an extreme degree of pallor and degenerations of the cord, about to be described.

Microscopic Examination.—Brain and cord examined. Stained by Weigert hematoxylin; phosphotungstic acid-hematoxylin; hematoxylin-eosin; Nissl.

The degenerations in this case involve chiefly the dorsal and lateral columns, and approach more to the type of a true combined neurone degeneration than the cases already described.

Lumbar Enlargement.—The degenerated areas of the cord are confined to a narrow area on either side of the dorsal septum, and to the region of the pyramidal tracts. The nerve roots show occasional patches of degeneration not of the neurone type. The lower thoracic region shows a dense neuroglia sclerosis of the dorsal columns, much more extensive than in the lumbar enlargement, sparing the root zones and a narrow strip on either side of the dorsal septum (Flechsig's oval bundle?) and along the dorsal periphery. The region of the pyramidal tracts shows a degeneration somewhat less in degree; nerve roots, normal.

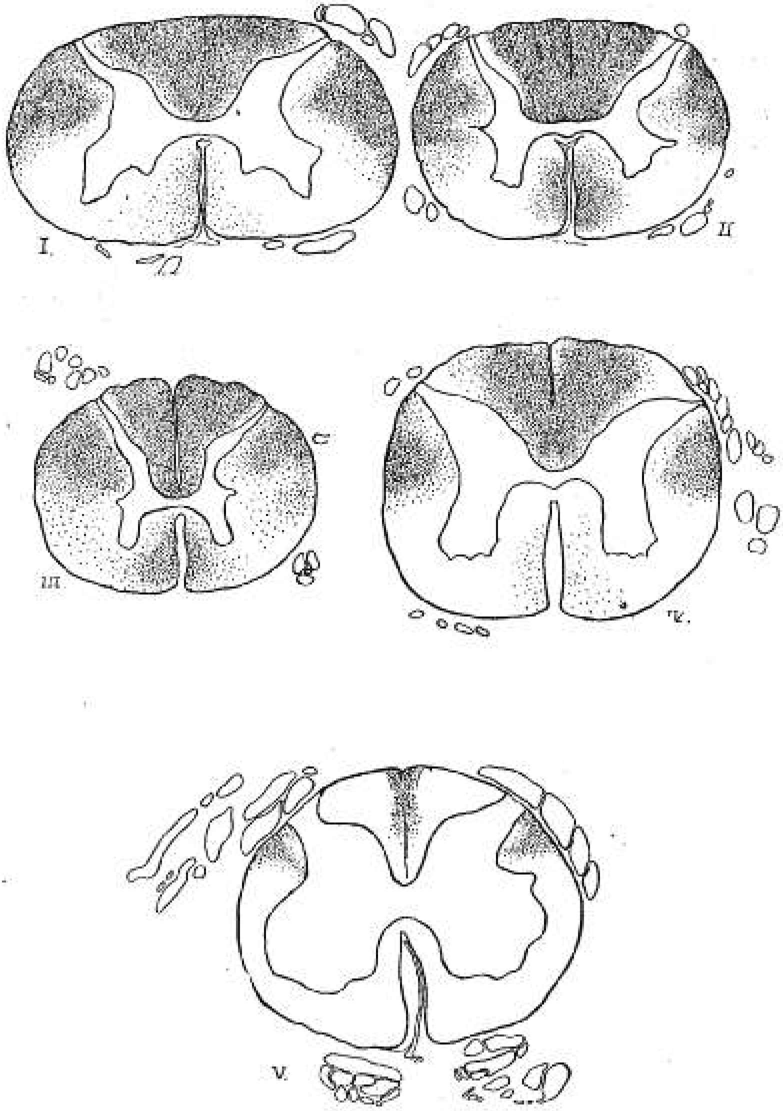
Thoracic Region.—Similar degenerations to those just described, but more extensive, and in the lateral columns extending beyond the areas of the pyramidal tracts. The ventral columns bordering the fissure are also irregularly degenerated. The upper thoracic region shows a similar distribution of the degeneration, but more extensive; the direct cerebellar tract is involved. Nerve roots and the dorsal root zone are intact, as are also fibers of the dorsal commissure.

Cervical Region.—The degenerations here are slightly less extensive than in the upper thoracic region, but are fairly sharply limited to the same general areas.

Oblongata and Pons.—The dorsal columns show a continued degeneration into the oblongata, which, however, does not include an involvement of the secondary (fillet) neurones. There are also occasional small areas of degeneration, which have no relation to recognized neurone systems. The pons shows no noteworthy abnormality.

Gray Matter.—Beyond hyperpigmentation in many cases, the ventral horn cells of the lumbar and cervical enlargements show no abnormality (Nissl). The same is true of the cells of the paracentral lobule of the brain. In some few cells the staining is slightly diffuse, and the pigmentation excessive, but most of them show a normal staining nucleus and distinct Nissl bodies.

Blood Vessels.—A slight hyaline thickening of the walls of the smaller vessel is observable in the degenerated areas. There is no general arterio-sclerosis.



Diagrams of the Spinal Cord from Case V.

Neuroglia.—In this case the overgrowth of neuroglia in analogous to that seen in diseases of the ordinary degenerative type. In the degenerated areas there is, almost without exception, a dense compensatory hypertrophy of the neuroglia.

Summary.—Diffuse degeneration chiefly of dorsal and lateral tracts of the cord, simulating a true combined neurone degeneration, more marked in upper than in lower segments of the cord; essentially normal nerve roots; slight involvement of oblongata; slight hyaline degeneration of vessel walls within the cord.

The five cases reported above undoubtedly belong to a distinct group of pathological processes, chiefly involving the cord, and rendered familiar during the past decade by the work of Lichtheim,[1] Putnam,[2] Dana,[3] Minnich,[4] Nonne,[5] Bastianelli,[6] and most recently, Russell, Batten, Collier.[7] Many other observers[8] have reported individual cases until the literature has grown to the point of establishing a lesion, which must hereafter be given a much more important place in the pathological anatomy of the nervous system than has heretofore been accorded it. To this end it seems desirable to report pathological findings with a considerable degree of care, and to determine as far as possible the characteristic features of the process under consideration. A tendency is already evident to subdivide the lesions thus far described into two classes, with relation to certain etiological factors, notably anemia. Many more observations are necessary before anything definite may be said on this point. In the meantime it is important to show that a process, distinct in certain essential particulars from other degenerative changes of the cord, occurs as the result of or associated with morbid physical conditions, which are as yet vague, and of which one may be anemia. It was this service which Putnam, followed by Dana, rendered in 1891. Lichtheim's preliminary work related to pernicious anemia, rather than to the broader question of cord changes following cachexias (toxemias?) of various sorts, and as such is hardly to be regarded as the forerunner of the broader field of investigation upon which we have now entered.

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[1] Lichtheim: Verhand. des Congresses für Innere Medicin, 1887, p. 84.

[2] Putnam: Jour. Nerv. and Mental Dis., Feby., 1891.

[3] Dana: Jour. Nerv. and Mental Dis., XXVI, p. 1, Jany., 1899, and several preceding papers.

[4] Minnich: Ztschft. für klin. Med., XXI, 1892, pp. 25, 265, and XXII, 1893, p. 60.

[5] Nonne: Arch. für Psych., XXV, 1893, p. 421.

[6] Bastianelli: Bull. d. R. Acad. Med. d. Roma., 1895-6.

[7] Russell, Batten, Collier: Brain LXXXIX, Spring, 1900, p. 39.

[8] See Russell, Batten and Collier paper for a full and recent bibliography.

Classification and Nomenclature.—It is desirable for the sake of accuracy and further progress that a classification of the lesions under discussion should be made. This has as yet by no means been attained, due, no doubt, to a variety of causes. Chief among these was the insistence which had previously been laid upon so-called combined system diseases, through the work of Westphal and others, with the assumption that these disorders were as truly "systemic" in distribution as tabes, for example. Ormerod[9] in 1885 published a critical digest on the "combination of lateral and posterior sclerosis of the spinal cord," in which he said that a multiple tract disease had been recognized, and also a sclerosis of columns not coinciding with known tracts, though too regular to be called in "the strictest sense diffuse." It is also of particular interest to note that Gowers,[10] in his now classical lecture on ataxic paraplegia made certain statements in his description of the pathological anatomy of the condition, which bring it much more into the category of a diffuse lesion than of a systemic neurone degeneration in the modern sense. For example, he says that the posterior and lateral columns are both affected, but often less intensely in the lumbar than in the dorsal cord; that the root zone is less affected than in tabes; that at times the degeneration does not reach the posterior periphery of the cord; that the degeneration of the lateral columns is not often "systemic in character." In the light of the neurone theory it is likewise clear that from Gowers' description the degeneration of the posterior columns is also not systemic in character. Whether or not, in fact, a true combined neurone degeneration of the lateral and dorsal tracts exists is a matter which the present investigation does nothing to elucidate, but it is clear that many cases of so-called ataxic paraplegia are due to a much more extensive lesion than the symptoms alone would warrant us in assuming.[11] At the same time it is at once to be admitted that the lesions observed in the class of cases under discussion have a quasi-systemic character, inasmuch as with practical constancy the dorsal and lateral columns are involved. It becomes necessary, therefore, to distinguish sharply between systemic in the old sense (Charcot) as applied to the cord alone, and systemic in the new sense as applied to nerve cells (neurones). The latter terminology, which is now alone admissable, is certainly excluded in these types of diffuse degeneration, and quasi-systemic, merely as a descriptive term, may alone be correctly employed. In 1891 Putnam used the term "system sclerosis of the cord, associated with diffuse collateral degeneration." Dana's former view was that Gowers' cases of ataxic paraplegia were "aberrant or complicated forms of tabes, transverse myelitis or multiple sclerosis,"[12] a view to which he no longer adheres. Russell, Batten and Collier[13] have reopened the discussion of the matter in their latest paper, by questioning the justifiability of the name, which, however, they finally adopt, as less likely to lead to confusion than a more accurate one would be. The title of their paper is "Subacute Combined Degeneration of the Spinal Cord." They deprecate the use of the word "combined" as inaccurate, and too wide in its significance, but think that "subacute" will sufficiently differentiate this from other forms of disease with which it might otherwise be confused. This, so far as we know, is a new terminology, and one which is not sufficiently exact to command a permanent place in the literature. The use of the word subacute, for example, gives no idea of the extent of the pathological process, and is no doubt used merely in a clinical sense. Putnam's original "System sclerosis, associated with diffuse collateral degeneration," is a more accurate designation, though perhaps unnecessarily long. We would suggest the simple term, "Diffuse Degeneration of the Spinal Cord." This terminology has the following advantages: It describes a process rather than a symptom; it is short and sufficiently descriptive; it distinguishes the lesion from myelitis, and lays stress upon the fact that it is an undoubted degeneration; it emphasizes the essential feature of the process, namely, its diffuse character, thereby removing the lesion from the so-called combined degenerations, where, as now generally admitted, it certainly does not belong. The term, furthermore, is sufficiently distinctive of a special pathological condition and should lead to no confusion. It may be that a further etiological subdivision of the group of cases may be necessary as our knowledge grows. In the meantime the most accurate provisional classification, which conflicts least with what has gone before, seems to us to be to regard the lesions as primarily degenerations and not inflammations, and as essentially diffuse rather than systemic in character.

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[9] Ormerod. Brain VIII, 1885, p. 110.

[10] Gowers: Lancet, July 3, 10, 1886, pp. 1, 61.

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[11] See also Leyden, Goldscheider, "Erkrankungen des Rückenmarkes," 1895, p. 97 in Nothangel series. These writers are inclined on anatomical grounds to deny the usefulness or correctness of the term "combined system disease." See also Leyden: Ztschft. für klin. Med., XXI, 1892, p. 1. "Ueber Chronische Myelitis und die Systemerkrankungen im Rückenmark."

[12] Dana. *loc. cit.*, p. 14. Dana's late terminology (Report at International Congress of Medicine, Paris, 1900), "Subacute Spinal Ataxia" is open to criticism from the fact that it lays stress upon a single symptom, and that not a constant one.

[13] Russell, etc., *loc. cit.*

Pathological Anatomy.—The features common to the general group of lesions are:

1. A diffuse degeneration for the most part limited to the cord, often in more or less discrete patches.
2. A constant involvement of the dorsal and lateral columns, without strict regard to neurone systems.
3. A predominance of the lesion in the cervical and thoracic regions.
4. The common freedom from degeneration of nerve roots, both motor and sensory, and peripheral nerves.
5. The practical non-involvement of gray matter.
6. Insignificant vessel changes.

A striking peculiarity in two of the cases, described also by several other observers, is the character of the degeneration, vacuolation with slight neuroglia proliferation. The occurrence of the degeneration in discrete areas, varying from segment to segment, is particularly characteristic, and does not occur in the same manner in any other condition. The work which has gone before and the many accurate descriptions of the pathological anatomy of the condition under consideration renders a repetition here wholly superfluous. A comparison, however, of our findings with certain features of the findings of preceding writers is desirable. Putnam's[14] paper, carelessly overlooked by many of the subsequent European writers, marks the beginning of the recognition of these diffuse lesions as due to a variety of causes, usually characterized clinically by general cachexia, and not solely by the existence of pernicious anemia (Lichtheim). The similarity of the lesions observed by Putnam to those noted by subsequent writers is clearly apparent from a review of the literature. The variations are, for the most part, in matters of unessential detail. Putnam and most recently Russell, Batten and Collier[15] are inclined to consider that the process is partly systemic in character and partly diffuse. Putnam finds "a relatively chronic sclerosis in the posterior and lateral centripetal and centrifugal long tracts" and also "a more acute and recent degenerative change in adjoining areas, partly diffuse and partly systemic in distribution." Russell and his colleagues affirm that there are "obviously two distinct processes at work in relation to the alteration found in the spinal cords of these cases: 1. A local destructive lesion. 2. A system lesion." So far as our observation goes there is no necessity for the assumption of a double process; it is rather the same process manifested with varying degrees of intensity in different regions of the cord. Unquestionably the dorsal and lateral tracts show the deepest degeneration, due, no doubt, to causes of which we have as yet insufficient knowledge, but it is too great an assumption to regard this as an evidence of two distinct processes. Furthermore, the degenerations of these areas, however topographically at given levels of the cord they may appear systemic, clearly do not represent neurone degeneration, to which, as already urged, the word systemic should now alone be applied. This is shown, for example, by the fact that the dorsal nerve roots are usually not degenerated, nor is the dorsal root zone, nor the pyramidal tract of the lower cord segments in many cases. It seems to us, therefore, both more conservative and most in accordance with the anatomical appearances to consider that we are dealing with a diffuse process, having no regard to actual neurone systems and at most merely quasi-systemic in character. Putnam also found in his original work on the subject a "degeneration of moderate degree in the nerve roots and peripheral nerves," a finding which subsequent investigators for the most part do not substantiate. In our five cases the nerve roots were remarkably free from degeneration. In Case III (Plate II, Fig. 4) the dorsal roots show occasional areas of degeneration (see also description of microscopic appearances) which are clearly not of the neurone type, but rather suggestive of some relatively slight, possibly vascular, disturbance. To this we would attach considerable importance as perhaps throwing light on the character of the cord process. Our somewhat meager observations would also tend to confirm the generally accepted opinion that peripheral nerves are only exceptionally involved to the extent of visible degenerations. The gray matter, likewise, is usually spared; what changes we have observed are slight and uncharacteristic, consisting essentially in over-pigmentation of ventral horn cells.

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[14] Putnam: *loc. cit.*

[15] Russell, etc., *loc. cit.*

If the extensive degenerations are due to vascular causes, certainly the objective appearance of the vessels gives no basis for this assumption. The larger vessels are in all cases normal, and the smaller show only occasional hyaline degeneration, standing in no discoverable relation to the areas of degeneration. It is, however, to be said that Nonne[16] found at times an evident relation of diseased vessels to areas of degeneration, a fact noted also by Minnich. In these instances the hyaline change was limited to the capillaries.

Pathological Histology.—A study of the minute changes in the diffuse degenerations is of importance in view of possible errors in pathological diagnosis. It is to be distinguished from true system diseases, a matter already sufficiently discussed; from myelitis; from multiple sclerosis; from simple softening. There is a tendency, still strongly observable, particularly among older writers (*e. g.*, Leyden), to use the term myelitis in a very general sense, quite regardless of any evidences of inflammation; the words subacute or chronic are commonly employed as modifying adjectives to describe varieties of this so-called myelitis. This tendency should be combated. There is ample evidence to show that a true myelitis exists which has all the histological appearances of a true inflammation; it is unnecessary to apply the term to conditions in which the histological appearances do not show evidences of inflammation. We also know that primary degenerations are of common occurrence in the nervous system (tabes; amyotrophic lateral sclerosis), similar to parenchymatous degenerations in other organs. The lesions under consideration have merely the appearances of a non-systemic primary neurone degeneration, not dependent upon an antecedent inflammation (myelitis). It seems desirable, therefore, to take the diffuse degenerations out of the vague category of myelitis and consider them simply as degenerations, until our knowledge of their etiology permits of a more accurate classification. The term myelitis implies a causative agent not yet proved to exist. The differentiation from multiple sclerosis should offer no difficulties. The areas of degeneration are not discrete; they show a constant quasi-systemic grouping; they are not characterized by a primary overgrowth of neuroglia. Simple softening, although it may no doubt occur in the progress of the disease (Putnam, Dana) is certainly not the essential process. There is no evidence of the occlusion of vessels, the contour of the cord is not altered, the process shows evidence of chronicity, and histological signs of softening are lacking. Appearances worthy of special note in the process, apart from the distribution of the lesions, are the character of the myeline degeneration and the behavior of the neuroglia. Individual nerve fibers are much swollen, the myeline sheath is stretched, as it were, giving the appearance of a vacuole, in which not infrequently a relatively normal axone may be distinguished. This vacuolated appearance (Plate I, Figs. 1, 2; Plate II, Fig. 3) is no doubt to be explained by the rapidity of the degenerative process.[17] The excessive number of fatty cells (Plate I, Fig. 1) furthermore bears out this supposition. This vacuolation of nerve fibers has been frequently described before, and derives its main interest from the fact that it is an index of the manner of development of the pathological process, and possibly may have a bearing on the occasionally observed rapid exacerbation of symptoms. We are not able, however, from the pathological appearances to account for the division of the clinical symptoms into three distinct stages, as given by Russell, Batten and Collier.[18] In some instances a perfectly typical neuroglia sclerosis, as seen, for example, in a late stage of tabes, is observed side by side with a rapidly progressing process of the type just described. The behavior of the neuroglia is of interest from the fact of the small tendency to proliferate frequently shown. This is no doubt due in part to the rapidity of the whole degenerative process (Nonne). It is furthermore possible that the general impoverishment of the part through poor or vitiated blood supply may so far reduce the vigor of the neuroglia that its normal compensatory hypertrophy is impossible. The same cause, in other words, which leads to the primary nerve degeneration may also prevent the growth of the neuroglia.

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[16] Nonne, *loc. cit.*

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[17] A similar appearance, though much less marked, we have observed in the cord from an early stage of tabes, the patient dying of an intercurrent disease.

As we have already indicated, it seems to us too soon to make either clinical or pathological divisions in the general group of diffuse degenerations, and particularly to attempt the demonstration of lesions peculiar to anemia. Bastianelli,[19] for example, has maintained that in cases due to pernicious anemia, the sclerosis is not so compact, and the lateral columns are little affected. Russell and his colleagues, who are in general sceptical of the etiological role of anemia, maintain that in no cases of fatal anemia have the changes found post-mortem been in any way comparable to those so characteristic of the subacute combined degeneration under discussion. From both of these views we must dissent. Our Case V. unquestionably died of pernicious anemia,[20] and showed post-mortem the most compact and sharply defined degenerations of any of our five cases. A finding which also does not tally with Russell's somewhat dogmatic statement.

Etiology.—The final and important question of the cause of the diffuse degenerations has been discussed in Dr. Putnam's clinical report. An excellent résumé of the matter is also to be found in Russell, Batten and Collier's paper, to which we have repeatedly had occasion to refer. We are in general agreement with the views clearly expressed by these writers that the peculiar and relatively constant distribution of the lesions in the cord depends upon the anatomical arrangement of the pial blood vessels, an idea first advanced for combined lesions by Marie. This in no way implies actual disease of the vessel walls with thrombosis, and consequent anemic necrosis, but simply that under the influence of a cause, as yet unknown, but probably toxic, those areas of the cord most deficiently supplied with blood under normal conditions, are likely to suffer first under abnormal conditions. The quasi-systemic character of the process is due to the proneness which certain long tracts are known to have to undergo degeneration from various causes, as observed, for example, in tabes or amyotrophic lateral sclerosis. It is clear that the field of future study in this, as in many other conditions of disease, lies in a discovery of the ultimate cause of the degenerative changes. Until this is done further classification may well be deferred.

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[18] Russell, etc., *loc. cit.* See also the foregoing clinical report.

[19] Bastianelli, *loc. cit.*

[20] The blood was examined during life by entirely competent persons, and the characteristic blood alterations found. The course of the disease was also characteristic.

The general conclusions derived from this study are:

1. That a well-defined lesion of the nervous system particularly localized in the cord exists, which may for the present be termed simply "diffuse degeneration."

2. That no fundamental characteristics of the lesion have been found depending on different causes.

3. That anemic states have been shown at times to be a concomitant condition, but not necessarily a cause.

4. That the actual causes are still wholly obscure.

Description of Plates.

Fig. 1. High power. Marchi, Van Gieson stain. Field taken in a rapidly degenerating area (Case II), showing vacuolated nerve fibers, very numerous fatty cells and disintegrating myeline, with unproliferated neuroglia.

Fig. 2. Weigert stain. Cervical cord; Case II, showing areas of degeneration. The line of undegenerated fibers between the columns of Goll and Burdach is noteworthy, also the sparing of the dorsal root zones.

Fig. 3. Weigert stain. Cervical cord; Case III, showing typical more or less discrete areas of degeneration. Nerve roots essentially normal.

Fig. 4. Same. Lumbar cord; degeneration limited to dorsal col-

PLATE I.

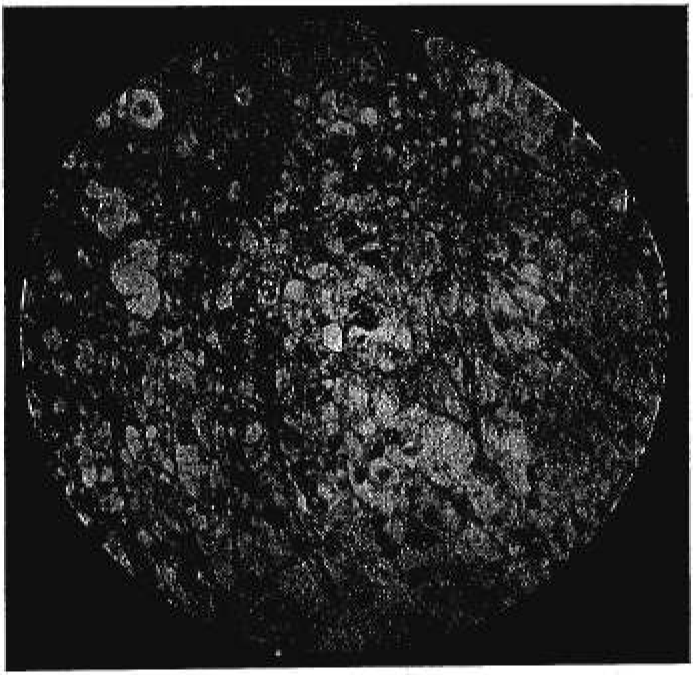


Fig. I.

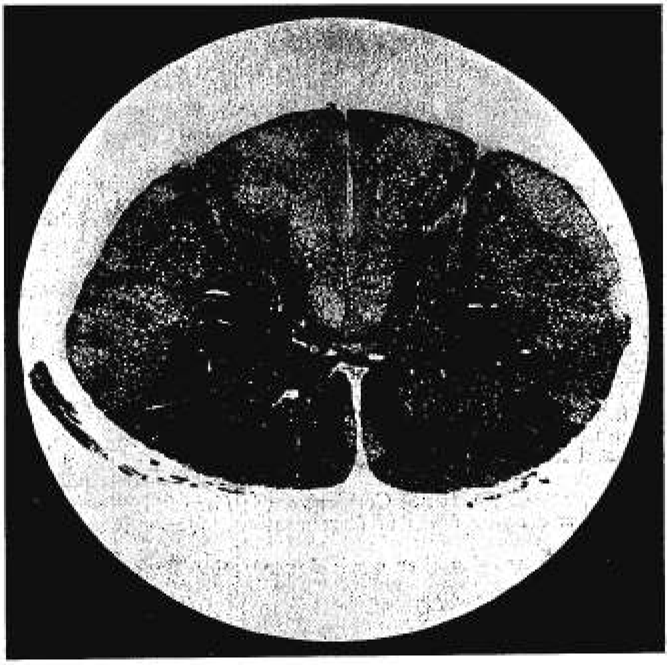


PLATE II.

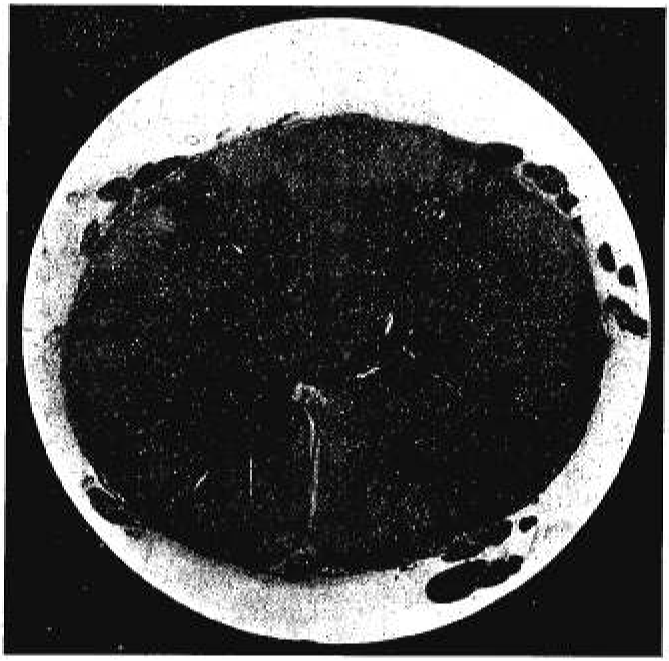
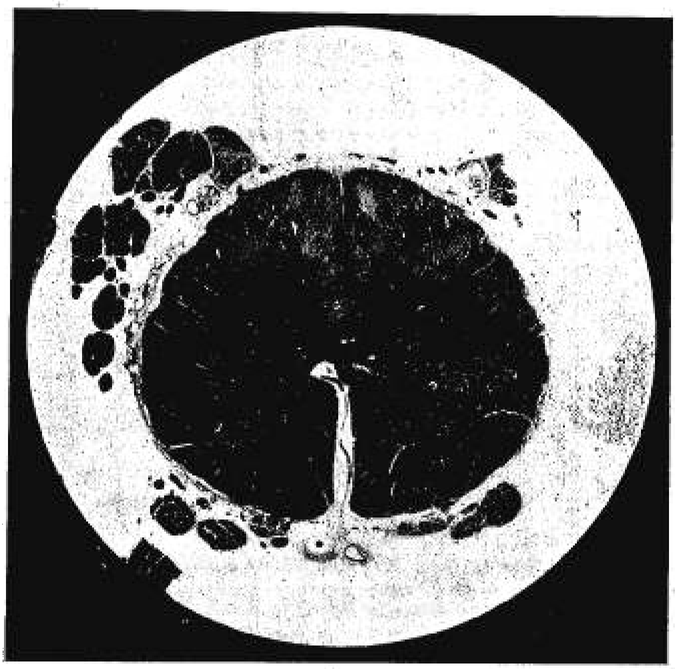


Fig. III.



umns. Patches of degeneration in dorsal nerve roots. Ventral nerve roots normal, though with low power there is an appearance of degeneration on the right side.

DISCUSSION.

Dr. Langdon said he had perhaps seen a half-dozen cases which he would have classified as postero-lateral sclerosis, in only one of which, however, had there been a blood examination. This one was a case of typical pernicious anemia and the cord was in process of study. According to his observations we have two groups of pernicious anemia—one with, the other without, this spinal degeneration. He had followed to the end a few cases of marked pernicious anemia, and had an opportunity to test them within a few weeks of death without the slightest evidence of symptoms that would indicate a lesion of the posterior and lateral columns.

He had also seen recently a lady of 38 years with a spleen extending down to Poupart's ligament and three inches to the right of the umbilicus, and her nervous symptoms were exceedingly vague. A most careful examination did not show any important, even functional, alteration. She presented a somewhat anemic appearance, not excessively so, but blood examination showed a spleno-myelogenous leukemia, with one white corpuscle to six or eight of red; and yet that patient came more than 15 miles to his office and did not consider herself very sick, except for the large spleen. These cases rather make the spinal symptoms in other patients embarrassing to explain.

He did not think that we can say that in every case of pernicious anemia we will necessarily have degeneration in the posterior and lateral tracts. This would suggest that these degenerations, when they do occur, are possibly the expression of a pre-existing degenerative tendency which is developed by the presence of the nutritional defect. The two are not necessarily associated with each other. That would be his own view of it from the cases that have been followed to the end without developing spinal symptoms.

Dr. W. G. Spiller asked Dr. Putnam to express a little more clearly whether he regarded these forms of degeneration that occur in pernicious anemia as systemic. There is a difference of opinion in regard to this point by those who have studied the spinal cord in pernicious anemia. Dr. Spiller wished to know how Dr. Putnam explained the degeneration of the posterior columns. The degeneration appeared to the naked eye to be systemic; and Dr. Putnam had stated in his remarks that the portions of the posterior columns, where the posterior roots enter, were not degenerated; and yet the posterior columns presented the appearance of ascending degeneration. Dr. Spiller was much interested in that subject at present and had been for some time. He had seen in several cases degeneration of the posterior columns without disease of the posterior roots and had found this also in amyotrophic lateral sclerosis, in the upper part of the thoracic cord. It has been supposed that in these cases the degeneration of the posterior columns is really a degeneration of the posterior roots, showing itself only in portions more remote from the cell-bodies. By others a degeneration of the posterior columns with integrity of the posterior roots has been regarded as an endogenous alteration. It was probable that if Dr. Putnam had had more time to present the paper by himself and Dr. Taylor, Dr. Spiller's question would have been unnecessary.

Dr. J. J. Putnam said he had as yet no positive opinion on the points which Dr. Spiller mentioned. Dr. Taylor thought that the nerve-roots did not suffer, the primary change being mainly or wholly in the cord. It has been maintained that these changes are focal and then coalesce, and that seems, in some cases, to be true, but on the whole Drs. Putnam and Taylor's specimens did not sustain this view as a general one. Posterior degeneration in the cervical region was very marked, but not universally greater there than elsewhere. The vessels were not much altered and the reference of the posterior degeneration to the fact that the circulation in the posterior column of the cord is less than that in the ventral part would not be a perfectly satisfactory explanation, for occasionally the uncrossed portion of the antero-lateral tract is involved, in spite of being in the more vascular part of the cord.

Dr. M. Prince said he was permitted to see these sections before coming to the meeting and got the impression from them that the areas of degeneration, in the posterior column, for instance, were not continuous throughout the whole column, but at certain levels the degeneration became limited or ceased, and then at a different level appeared again, and so on. This would seem to negative the idea of the disease being one of the regularly recognized system diseases and would bear out Dr. Putnam's view of the pathology. He would like to ask Dr. Putnam whether this was not so.

Dr. J. J. Putnam said he could not speak definitely, but the clinical symptoms seem to show that we have to deal in these cases with a special disease which is just as definite as tabes. The anatomical lesions are not explained. In one case of thirteen years' standing they were very slight indeed.